REMARKS

Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 45, 46, 62, 70, 78, 94, and 96-110 are pending in this application. Claim 62 is rewritten as an independent claim including all limitations of previously pending claim 45. Claim 45 is amended to render it clear that the mutants are those that exhibit increased Rep activity, manifested as increased titer of AAV at 37° C. Basis for such is found throughout the application, which describes preparation of AAV under such conditions. For example, the application states that mutant AAV virus for titering were produced by the triple transfection method (see, *e.g.*, page 43, lines 9 and 10). The application references and incorporates by reference (see, page) Drittanti (2000) *Gene Therapy 7*:924-929, which describes the triple transfection method, virtually word-for-word the description on page 43, and states, see *e.g.*, Figure 3, and states that replication of AAV is assessed at 37° C (see, *e.g.*, page 927, col. 2). Furthermore, references incorporated by reference that discuss production of AAV in HEK 293 cells, indicate that cells are grown at 37° C (see, *e.g.*, Wu *et al.* (2000) *J. Virol. 74*:8635-8647). Also is clear from the application that Applicant contemplates assessing AAV replication at 37° C, since no other temperature is mentioned, the standard method referred to in the application, the triple transfection method is performed at 37° C.

Claims 105-110 are added. Basis is found in the original claims. Particular basis for claim 105 is found in the specification which indicates that to produce the mutants, all codons are replaced with codons encoding alanine to identify hits, which refer to any mutants that alter titer. As described in the application, every amino acid residue in the Rep proteins was replaced one-by-one with alanine to identify hits, and none of these exhibited increased activity. Hence, replacement of amino acid residues with alanine does not yield Rep proteins that result in viruses with higher titer.

Claim 108 recites that the mutations are not temperature sensitive. As discussed previously, a negative limitation added to exclude the prior art **is not new matter.** US caselaw recognizes this principle. Where a disclosure recites a species within a genus and that species is later sought to be excluded from the claims, the written description requirement is satisfied. See *In re Johnson*, 194 USPQ 187 (CCPA 1977). In Johnson, the Court of Customs and Patent Appeals held:

> It is for the inventor to decide what bounds of protection he will seek. In re Saunders, 58 CCPA 1316, 1327, 444 F.2d 599, 607, 170 USPQ 213, 220 (1971). To deny appellants ... would, as this court said in Saunders: 'let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species because he erroneously thought he was first with the genus when he filed.'
>
> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species there within, has somehow failed to disclose, and teach those skilled in the art how to make and use the genus minus two of the species, and thus has failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. Id at 196.

See also In re Driscoll, 195 USPQ 434 (CCPA 1997) (holding that a claim to a single species was supported by the specification, where the specification recited a Markush group that included the claimed species along with other species not included in the claim). Hence, amending the claim to exclude temperature sensitive mutants, is not new matter.

Also, with respect to claim 108, no mention in the specification is made of temperature sensitive mutants, nor did applicant consider comparing activity wild-type activity at a temperature at which the wild-type activity would be reduced. The purpose in the rational directed evolution of the Rep proteins is to increase titer, the actual amount of AAV made. A TS mutant, by definition, would make more of something at the non-permissive temperature compared to the wild-type, but it does not make more than wildtype under conditions for growth of wild-type. It makes no sense in the context of this application, which is describes identification of mutants that yield increase titer that such is a relative amount. The mutants of Gavin *et al.* do not yield virus with increased titer, but only increased titer when compared to wild-type at the non-permissive temperature. The mutants of Gavin *et al.*, even when grown at 32 ° C do not result in increased titer of virus compared to wild-type, when wild-type is grown at a permissive temperature. This is a situation in which semantics and form over substance should not control. Clearly, the instant applicant did not contemplate mutants that produce more virus at 32 ° C than wild-type does at 32 ° C; such would not achieve the purpose of make more AAV. Therefore, applicant should be permitted to amend the claims, such as by reciting that production is performed at 37° C, or the mutations are not temperature-sensitive, to avoid inadvertently encompassing unintended species.

Further as discussed in the previous response, the application renders it clear that standard conditions, such as 37° C, the temperature at which cells are grown and AAV is ordinarily produced, are contemplated. There is no discussion in the application that AAV replication would be performed at 32° C; less virus is produced at such conditions, and no one prepares virus at 32° C. The application, insofar as it is directed to AAV, is directed to identifying Rep mutants that result a real increase in titer, not a relative increase at a temperature that is suboptimal, at best, for the wild-type.. Such is implicit in the application (see e.g., *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973); also see e.g., *In re Saunders*, 444 F.2d 599, 607. 170 USPQ 213, 220 (CCPA 1971); *In re Johnson,* 558 F.2d 1008, 194 USPQ 187 (CCPA 1977).

Applicant respectfully submits that the instant specification is directed to nucleic acid molecules encoding mutant Rep proteins that result in high-titer rAAV stocks for use in, for example, gene therapy. A reading of the specification as a whole renders it clear that the mutant molecules result in a higher titer of rAAV compared to wild type encoded Rep proteins under conditions where the wild-type Rep proteins are tested, *i.e.* at 37 ° C, and comparisons between and among the mutant Rep proteins all were preformed under such conditions.

For example, the specification describes that a problem solved by the instant application "is a solution to the need in the gene therapy industry to increase the production of therapeutic vectors without up-scaling manufacturing," (see page 4 , lines 22-25) and that methods provided in the specification to identify mutant molecules "permit optimization of its activities as assessed by increases in viral production" (see page 28, lines 9-11). Clearly , this does not include production at 32° C, which is a temperature that one of skill in the art would not normally transfect mammalian cells and/or produce virus, and therefore is a condition which one of skill in the art would recognize to be improper for providing rAAV stocks with higher titers. Further, as discussed throughout the application, , all 566 mutants that were prepared were tested and compared to wild-type AAV were compared at 37° C, not at reduced temperature. Furthermore

> By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Accordingly, amended claim 45 recites that AAV production is effected at 37° C. As an alternative, claim 108 is added to exclude temperature-sensitive mutants. Claim 105 recites that none of the mutants has an alanine replacement. None of the 566 mutants tested and described in the application include an Ala mutation and result in increased titer. Thus, no new matter is added.

Restriction Requirement and Election of Species

Applicant acknowledges that claims 45, 46, 62, 70, 78, 94 and 96-110 are pending. As discussed previous, the Examiner, however, urges that the instant claims are under examination only with respect to the mutation identified in claim 62 as "T to N at position 350" represented by SEQ ID NO:113, since no generic or linking claim is found allowable. As described herein below, Applicant respectfully submits that claim 45 as amended, as well as claims 105 and 108, and all dependent claims, are **not** anticipated by the cited reference. As discussed previously, Applicant's extensive searches have never yielded any Rep mutations that actually increase the amount of AAV produced. Therefore, the generic claim is novel and inventive.

THE REJECTION OF CLAIMS 45, 46 AND 98UNDER 35 U.S.C. §112, FIRST PARAGRAPH – WRITTEN DESCRIPTION NEW MATTER

Claims 45, 46, and 98 are rejected under 35 U. S. C. 112, first paragraph, as failing to comply with the written description requirement because it is alleged that amendment of the claims to recite language "standard conditions" adds new matter. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks. As amended herein, the language "standard conditions" has been deleted, thereby rendering this ground for rejection moot.

As discussed above, it is **not new matter** to amend the claims to exclude a species that is inadvertently included a claim. Claim 108 excludes temperature-sensitive mutations.

Claim 105 excludes alanine as a replacing amino acid. As shown in the application, none of the 566 species tested that included an Ala in place of a native amino acid exhibited increased titer. Hence, there is basis in the application for reciting that the mutant does not include Ala as a replacement.

Claim 45 is amended to render it clear that AAV production is performed at 37° C so that the increase is an absolute increase in AAV production. In Gavin *et al.*, the TS mutant did not produce more AAV at the 32° C than wild-type at its temperature; it only produced more at 32° C, a temperature at which wild-type does not replicate effectively.

THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, FIRST PARAGRAPH – WRITTEN DESCRIPTION- POSSESSION

Claims 45, 46, 62, 70, 78, 94 and 96-100 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that Applicant was not in possession of the full genus because the claims encompass a wide and variable genus of nucleic acid molecules, the structure of which is not sufficiently disclosed in the specification and the claims. This rejection is respectfully traversed for the reasons of record. The Examiner's arguments addressing these reasons are rebutted in turn.

As discussed previously, the application identifies and provides examples of at least 6 species of nucleic acid molecules encoding mutant REP proteins that when expressed result in AAV with higher titer. The specification provides detailed description how to isolate and prepare additional species that have the requisite property. In addition, the specification describes preparation of and testing and the results of testing of all hundreds of species in which each amino acid was replaced one-by-one with Alanine to identify hits, and then each hit replaced in turn with every other amino acid to identify hits that have the property of increased titer. Hence, Applicant likely ferreted out all of the residues that can be mutated to exhibit increased titer; if any are missing or if there are other combinations, the specification clearly teaches how to identify other such mutants. With regard to the various serotypes; they are allelic variants, with, as demonstrated and conceded by the Examiner, minimal variation. The specification identifies the residues in each of these variants that can be modified to exhibit increased AAV titer. There is no requirement in patent law to provide working examples of every single species within a claim. It is clear, that applicant had possession of the genus of molecules as required by 35 U.S.C. §112, first paragraph. The remarks of the Examiner are rebutted in turn below.

Relevant Law

Relevant law and a discussion of the Patent Office Guidelines are set forth in previous responses of record.

The claims

Claim 45 is directed to a nucleic acid molecule that encodes a mutant AAV Rep protein, in any AAV serotype of AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4 and AAV-6, that has *increased* activity as manifested as an increased titer of virus upon introduction and replication of virus at 37° C in a host cell containing in its genome nucleic acid encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of virus

containing a wild type Rep gene. The claim specifies that the mutation is in the corresponding position in each serotype. Claim 62, rewritten as an independent claim, includes all limitations of claim 45, but also specifies the mutated positions so that recitation of 37 ° C is not required to avoid any possible interpretation that the claims encompass mutations that express at a non-permissive temperature for wild-type. Claims 105 and 108, include the recitation that replacements are not Ala, and that the mutation is not TS, respectively.

Analysis

The Office Action alleges that there is a lack of written description of the claimed genus of nucleic acid molecules encoding mutant Rep proteins having increased activity. It is alleged that insofar as the genus of nucleic acids encoding for mutant Rep proteins is very large and a great deal of variability is encompassed by the instant claims, the claims encompass within their breadth any nucleic acid encoding for a mutant Rep protein that has increased activity. In particular, the Examiner urges that the genus is described by its function to affect viral replication, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Accordingly, it is alleged that Applicant is not in possession of the claimed subject matter at the time the application was filed because the specification fails to provide the relationship between structure and function for the nucleic acids encoding the mutant proteins. Applicant respectfully disagrees. As discussed previously, Applicant tested hundreds of mutations and identifies positions in Rep proteins that result in increased titer. Further Applicant provides details for a systematic way to identify any further mutants that fall within the scope of the claims. It is eminently clear that Applicant was in possession of the claimed genus in compliance with 35 U.S.C. §112, first paragraph.

As discussed in the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (hereinafter the Guidelines), the written description requirement for a claimed genus may be satisfied through 1) sufficient description of a representative number of species by actual reduction to practice, 2) reduction to drawings, **or** 3) by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The guidelines, and the case law upon which they are derived, do not recite 1), 2) and 3) in the conjunctive, **but in the alternative.** No where in the guidelines, case law or elsewhere in the patent laws, must one provide 1), 2) **and** 3). As discussed above, and previously, applicant tested every position, one-by-one, in the Rep proteins and identified those the alter AAV titer, and, for those, identified amino acid replacements that result in increased titer. Further, the specification even identifies the corresponding mutations in the highly conserved serotypes. In view of the specification, the skilled artisan is directed to positions to be modified, and is taught, in detail, how, if needed, to identify any other positions. There is no structural feature that can be identified; the instant claims are not directed to an improved doorknob, but to modified proteins, whose structure is based on its constituent amino acids. Applicant tested **all** of them for serotype and provides the results in the application. Applicant can do no more.

As discussed previously, the application describes more than a representative number of species by actual reduction to practice, the application provides the results of testing every residue to identify those that alter titer, and to identify specific replacements that result in increased viral titer. The specification provides the sequences of such molecules and corresponding positions in other AAV serotypes. The application tested **every amino acid locus** to identify **all** whose change results in a change in titer. Every replacing amino acid was tested. Hence the application provides a detailed description of the relationship between the structure and functioning of Rep proteins as assessed by assessing viral titer. Based on this property and using the methods described in the, the application teaches how to identify any additional species within the scope of the claim and how to assay or test combinations of mutations. The application describes a method for preparing proteins that have predetermined properties and exemplifies it using the AAV Rep proteins. In fact, the application exemplifies an **entire genus** with respect to one serotype and identifies the corresponding mutations in all other AAV serotypes. Thus, Applicant possessed the claimed subject matter at least as of the filing date of the instant application.

As discussed below, the application provides a detailed description of identification and preparation of a representative number of such nucleic acid molecules encoding mutant Rep proteins, including detailed description and working examples and of the method for generating such molecules and testing such molecules. Furthermore, the specification provides methods for producing and testing additional modified Rep proteins and nucleic acid

molecule s encoding the same for increased viral titer. Hence, Applicant possessed the genus as claimed.

A. The specification provides sufficient identifying characteristics of nucleic acid molecules encoding mutant Rep proteins to evidence Applicant's possession of the claimed subject matter as of the filing date.

An adequate written description of a claimed genus need provide "relevant, identifying characteristics" sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention (MPEP §2163). The Enzo court stated that "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" Further, the Guidelines set forth that a relevant identifying characteristic can be stated in terms of a function. For example, the Guidelines state as follows:

> For example, if the art has established a strong correlation between structure and function, one skilled in the act would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of a function and minimal structure when there is a well-established correlation between structure and function. MPEP §2163.

In this instance, Applicant respectfully submits that the claimed nucleic acid molecules sufficiently are described based on an identifying characteristic shared amongst the genus of claimed molecules, i.e. the feature of increased viral replication. The specification describes in great detail how to identify such molecules, and exemplifies representative species, including their sequence, that exhibit this identifying feature. Applicant is providing mutants that have *increased* activity as manifested by increased viral titer. The application tested every single position, using every amino acid replacement at each locus, in one serotype and tested the effect on the resulting AAV viruses. Hence for AAV-2, every member of the genus is identified and tested. The application was prepared and tested every combination of modified amino acid (see, *e.g.*, the Example and Figures) for each of the Rep proteins and identifies the loci that contribute to changes in viral titer. The application further identifies those loci and amino acid changes the result in increased titer. Further, the application identifies the corresponding loci in all AAV serotypes. In addition, the

application teaches how to prepare additional mutants and test them. The application provides the structure/function relationships.

The application provides a very detailed description of how to modify Rep encoding nucleic acids, and, in fact modifies every single amino acid in the proteins one-by-one and tests the effects The application teaches (see, *e.g.*, page 28) that the Rep protein(s) are involved in replication and are the target for the methods in the application for increasing viral production. As stated in the application (page 28), the methods in the application permit optimization of the activities of Rep as assessed by viral production. The methods tested every amino acid locus on the Rep protein and identified those that lead to a change in activity (i.e. those relevant for viral replication). The alanine scan across the full length of the Rep-encoding nucleic acid molecule identified hit loci. Each hit locus was replaced with the 18 remaining amino acids one-by-one; each molecule was tested one-by-one, so that each locus and amino acid change leading to increased titer was identified (see *e.g.*, page 29 *et seq,* the Example, and Figures 2 and 3; amino acid sequences of all Rep proteins are set forth in SEQ ID Nos. 1-562 and 726-728 and of the nucleic acid molecules SEQ ID Nos. 563-725) The application describes assays for assessing titer. In both rounds of testing each mutant was individually designed, generated, processed and tested. Page 31, for example, summarizes the results, identifying all hit positions for reach of the Rep proteins. The application identifies, for the first time, mutations, including replacing amino acids, that increase viral titer (under standard conditions) and identifies

The specification describes in great detail the generation of and testing of nucleic acid molecules encoding mutant Rep proteins for viral replication to identify those that encoded proteins that resulted in an increased viral titer. For example, the specification describes a mammalian cell-based expression based assay to phenotypically characterize the mutants for effects on viral titer. The specification describes all the necessary components of the assay used to generate recombinant (rAAV) viruses containing nucleic acid molecules encoding the mutant Rep proteins, and the assessment of the viral titer of the produced rAAVs. For example, the specification describes the generation of rAAV viruses by the co-transfection of mammalian cells with three plasmids: a plasmid encoding the mutant Rep proteins, a plasmid encoding AAV necessary proteins and DNA and an rAAV plasmid vector that provided the necessary signaling and substrate ITR sequences.(at page 30, line 1-14). The specification further describes the assessment of viral titer of each rAAV generated by determination of the number of infection particles (ip) produced by each rAAV upon introduction of the virus into

a mammalian cell using either a reporter gene (i.e. bacterial lacZ) or real time (RT)- PCR readout (see e.g., at page 30, lines 21-24). This is exemplified in the Example. Other assays for the determination for viral titer are known to one of skill in the art. The specification, including the Example, describe the testing of a variety of nucleic acid molecules encoding mutant Rep proteins and exemplify 12 clones having increased activity as manifested by increased viral replication (see e.g. Figure 2B).. The specification describes the corresponding position of the encoded mutations in each of the seven AAV serotypes.

The specification clearly describes that other mutants and other combinations of mutants can be generated and identified. For example, the specification at page 33, lines 3-8 states:

> Other combinations of mutations can be prepared and tested as described herein to identify other leads of interest, particularly those that have increased rep protein activity or that result in higher viral titers in cells containing such viruses that include appropriate cis acting elements for viral production.

Hence, the specification clearly set forth that Applicant had possession of a genus of nucleic acid molecules encoding mutant Rep proteins exhibiting effects on increased viral titer, and that such molecules could be identified by testing for viral activity.

Hence, the instant application clearly describes a genus of nucleic acid molecules encoding mutant Rep protein having a relevant identifying characteristic of increased activity as manifested by effects on increased viral titer. Because the specification adequately describes how one may (i) identify and select molecules that provide increased activity; (ii) generate the molecules; and (iii) measure a specific effect, namely effects on increased viral titer, Applicant had possession of the claimed subject matter at the time of filing the application.

B. The specification exemplifies more than a reasonable number of species

Applicant is not required to provide a representative of everything claimed but may show possession by providing identifying features common to all members. As described above, Applicant, by way of detailed descriptions of features, working example, and exemplary molecules, has done exactly that. Accordingly, Applicant respectfully submits that the specification sets forth a representative number of species of the claimed nucleic acid molecules, which species were actually reduced to practice, to evidence Applicant's possession of the claimed subject matter. According to the Guidelines, a ``representative number of species" means that the species which are adequately described are representative of the entire genus. As discussed, the application describes assessing the effect of changing

each and every amino acid position with every amino acid, and identifies those that result in increased titer and identified every position that contributed in increased titer and then identified the corresponding positions in all AAV serotypes. Applicant can do no more. The specification provides 12 loci in nucleic acids encoding mutant Rep proteins, that result in increased viral titer, Further, the specification sets forth corresponding mutations in each of the other AAV serotypes, thereby providing no less than 70 species of nucleic acid molecules encoding a mutant AAV Rep protein that have increased activity. This is based on testing and exemplifying 566 species.

Further, the Guidelines state the following:

> What constitutes a ``representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.

It respectfully is submitted that one of skill in the art would conclude that, having tested all combinations of mutations and provided the data for such tests the description in the specification constitutes a sufficiently detailed description to evidence that Applicant's possession of nucleic acid molecules that encode Rep proteins that result in increased titer compared to wild-type under standard conditions.

. As discussed in each of the previous two responses, the Examiner has failed to indicate why one of skill in the art, who is in possession of the nucleic acid molecules encoding any one or more mutant Rep protein (via the overlapping nature of the reading frames), in view of the description in the specification of all of the tested species, including the Example, Figures 2 and Figures 3, which exemplify the sequence identity among AAV serotypes and corresponding positions, and of the methods for preparing and testing polypeptides for activity, in view of the extensive knowledge of those of skill in the art, would be unable to recognize, upon reading the disclosure, that Applicant has possession of the claimed subject matter at least on the day of filing of the priority application. The specification clearly exemplifies mutations in the AAV genome that result in increased viral titer,, and teaches in great detail how to generate other such species.

Rebuttal To Examiner's Remarks

1) The Examiner urges that Applicant traversed the instant rejection on the grounds that the specification. This is not correct. As discussed above, the Application describes testing of every amino acid along the length of each Rep protein to identify which residues alter titer, and then replaced each such residue to identify replacing amino acids that result in increased titer. Hence, it is possible that Applicant identified virtually ***all*** **of the species** in the genus. Clearly, at worst, Applicant identified a large percentage and taught how to identify others.

2) The Examiner urges that:

> Applicant argues that the application tested every amino acid locus to identify all whose changes result in a change in titer and therefore, the specification provides a detailed description of the relationship between the structure and function of Rep proteins, as assessed by the viral titer. Applicant asserts that, based on this property and using the methods as described, the application teaches how to identify additional species within the scope of the claims and how to assay combinations of mutations. Applicant argues that, since the specification exemplifies an entire genus with respect to one serotype and identifies the corresponding mutations in all other AAV serotypes, Applicant was in possession of the claimed subject matter as of the filing date of the instant application. Applicant submits that he is not required to provide a representative number of everything that is claimed, but rather show possession by providing identifying features common to all members. Therefore, Applicant requests the withdrawal of the rejection.

The Examiner, however, is not persuaded because:

> with the exception of the sequences disclosed mutations, the specification fails to describe additional representative species of the nucleic acids mentioned above. While it is true that the above mutations are expected to result in mutant Rep proteins with similar increased activity when applied the Rep proteins of other AAV serotypes (it is noted that the Rep proteins are highly conserved among the different serotypes), the claimed genus is much broader than this since it encompasses any other mutation(s)over protein lengths of approximately 620 amino acid residues, wherein the mutation(s)must result in increased activity. One skilled in the art would know that a change of even one amino acid residue in the claimed sequences could render an inactive protein or a protein with a diminished activity. It is noted that the art and the instant specification do teach that the majority of mutations in Rep protein sequence results in a protein with decreased activity or in a dominant negative Rep protein. Even in his arguments, Applicant admits that most of the mutations he tested did not result in a protein having an increased activity, as required by the instant invention. Applicant argues that the specification provides methods to mutate Rep and test the mutations or the combination of mutations; however, just by having a method to mutate and test does not mean that Applicant was in possession of the entire claimed genus, especially that, as indicated above, the majority of mutations does not render the desired activity. Even Applicant's argument that he tested substitution of every amino acid at every locus and identified only eight hits

> supports this assertion. It does not mean the specification teaches testing of 600 mutants and identification of 12 with activity and teaches how to test any others

Applicant respectfully disagrees. Since Applicant teaches the effect of each and every residue on AAV titer, Applicant demonstrates possession of the genus. The fact that most residues do not contribute to increased titer does not reflect a failure to possess the genus, but the biology of the proteins. The fact that Applicant did not test every single permutation and combination of the so-identified mutations and loci, does not denigrate from compliance with the written description requirement. One of skill in the art, if so-inclined, or if needed, can test particular permutations or combinations, just as taught in the application.

3) The Examiner goes on:

> The art clearly teaches that Rep proteins are divided into partially distinct functional domains that are spread throughout the protein length and that most mutations disrupt Rep function; therefore, one of skill in the art would know that not just any mutation would increase Rep activity.

Applicant tested the entire length of each of the Rep proteins to assess which residues affect viral titer. In light of the specification, one of skill in the art knows which residues affect viral titer and which do not. As stated above, Applicant reasonably could do no more. There is no requirement in patent law to test every permutation. There is no requirement in patent law to disclose every single species within the scope of a claim.

THE REJECTION OF CLAIMS 45, 46 and 94 UNDER 35 U.S.C. §102

Claims 45, 46 and 94 are rejected under 35 U.S.C §102(b) as being anticipated by Gavin *et al.* (J. of Virol., 73: 9433-9445 (1999), which allegedly discloses a nucleic acid molecule encoding a mutant AAV-2 Rep78, wherein the mutant Rep protein has increased activity and wherein co-transfection of the nucleic acid encoding the mutant Rep and recombinant AAV plasmid into 293 cells mediates increased viral replication compared to the wild type. This rejection is respectfully traversed.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent

on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The Rejected Claims:

The rejected claims are discussed above.

Independent claim 45 recites:

> A nucleic acid molecule that encodes a mutant adeno-associated virus (AAV) Rep protein that has increased activity, wherein:
> increased activity of the Rep protein is manifested as an increased titer of virus at 37° C upon introduction and replication of virus in a host cell that contains in its genome the nucleic acid molecule encoding the mutant Rep protein, compared to the titer of virus upon introduction and replication of a virus in a host cell containing a wild type Rep gene;
> the AAV serotype is an AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4 or AAV6 serotype; and
> the mutation is in the corresponding position in each serotype.

Independent claim 105 recites that the mutations are not Ala replacements, and independent claim 108 recites that the mutant Rep proteins are not temperature-sensitive.

Differences between the disclosure of U.S. Patent No. 5,785,970 and the rejected claims

Gavin *et al.* discloses mutations in adeno-associated virus type 2 Rep78/68 by alanine substitution to target a number of the functional domains critical for Rep-mediated activities, and describe the effect of these mutations on Rep78-mediated replication of an ITR-containing vector in adenovirus-infected human cells. In particular, Gavin *et al.* discloses that a charge-to-alanine substitution strategy is particularly effective **to generate temperature sensitive (ts) mutants**. Gavin *et al.* discloses a temperature sensitive (ts) mutant, D40,42,44A-78, resulting in increased viral titer at 32° C. This mutant is defective for replication under physiological conditions. The mutant mediated replication 3-fold more efficiently at 32° C compared to at 37° C, and was essentially inactive at 39° C. At the permissive temperature of 32°C, the effect of the mutant on viral replication was delayed in adenovirus type 5-infected HEK 293 cells transfected with a plasmid expressing the mutant as assessed by Southern Blotting for Hirt DNA at various time points. .

Gavin *et al.* discloses that ,while virus was detected at normal levels in the presence of a wild-type Rep gene, there was *little to no detectable virus replication* observed at 37° C or 39°C in the presence of the encoded mutant Rep protein. Furthermore, mutant Rep protein is temperature sensitive and includes Ala replacements.

Accordingly, the disclosure of Gavin *et al.* **does not** provide a nucleic acid molecule encoding a mutant Rep protein resulting in increased titer at 37° C (claim 45), nor a mutant that does not include Ala (claim 105), nor a mutant that is not temperature sensitive (claim 108). Thus, Gavin *et al.*, does not disclose all elements as claimed in any of claims 45, 105, 108 nor any claim dependent thereon. Therefore, Gavin *et al.* does not anticipate any pending claim.

It is noted that even without amendment, Gavin *et al.* does not anticipate any pending claim, when the claims are read in light of the specification, which is directed to methods for producing AAV with increased titer (*i.e,* more AAV), and the AAV that exhibit increased titer. Gavin *et al.* discloses a TS mutant that results in production at the non-permissive temperature, but does not result in an increase in titer at any temperature. Therefore, Gavin *et al.*, does not anticipate the claims as previously pending.

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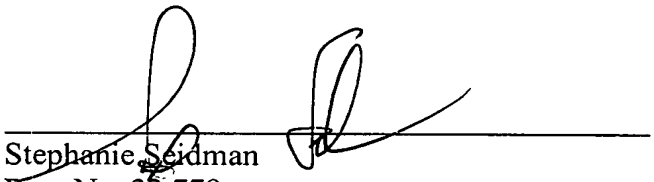
In view of the, amendments and remarks herein, reexamination and allowance of the application are respectfully requested.

Respectfully submitted,



Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 17109-003001/912
Address all correspondence to:
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com